Effects of amnesia on processing in the hippocampus and default mode network during a naturalistic memory task: a case study

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Effects of amnesia on processing in the hippocampus and default mode network during a naturalistic memory task: A case study

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Abstract:

Despite their severely impaired episodic memory, individuals with amnesia are able to comprehend ongoing events. Online representations of a current event are thought to be supported by a network of regions centred on the posterior midline cortex (PMC). By contrast, episodic memory is widely believed to be supported by interactions between the hippocampus and these cortical regions. In this MRI study, we investigated the encoding and retrieval of lifelike events (video clips) in a patient with severe amnesia likely resulting from a stroke to the right (and possibly the left) thalamus, and a group of 20 age-matched controls. Structural MRI revealed grey matter reductions in left hippocampus and left thalamus in comparison to controls. We first characterised the regions activated in the controls while they watched and retrieved the videos. There were no differences in activation between the patient and controls in any of the regions. We then identified a widespread network of brain regions, including the hippocampus, that were functionally connected with the PMC in controls. However, in the patient there was a specific reduction in functional connectivity between the PMC and a region of left hippocampus when both watching and attempting to retrieve the videos. A follow up analysis revealed that in controls the functional connectivity between these regions when watching the videos was correlated with memory performance. Taken together, these findings support the view that the interactions between the PMC and the hippocampus enable the encoding and retrieval of naturalistic events.

1. Introduction

Episodic memory is thought to be underpinned by interactions between the hippocampus and neocortex, at least over timescales of days and months (Marr, 1971; McClelland, McNaughton, & O'Reilly, 1995; Schapiro, Turk-Browne, Botvinick, & Norman, 2017; Teyler & DiScenna, 1986; Treves & Rolls, 1994). Several streams of research support this proposal. Focal damage to the hippocampus often results in dramatic impairment of episodic memory. Conversely, cortical lesions can cause impairments in perception, attention or semantic processing with little impact on memory function (Kolb & Whishaw, 2003). In the absence of major memory impairment, damage to lateral parietal regions implicated in memory can however cause a qualitative loss in the fidelity of episodic memory retrieval (Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007; Simons, Peers, Mazuz, Berryhill, & Olson, 2010).

Interestingly, focal hippocampal damage, and dense amnesia more generally, does not impair the ability to comprehend ongoing events whose content far exceeds short-term memory capacity for unconnected items, and which require the binding of attributes of multiple interacting stimuli within and across sensory modalities (Baddeley & Wilson, 2002; Chen et al., 2016; Squire, Stark, & Clark, 2004; von Cramon, Hebel, & Schuri, 1985). Thus, the binding together and representation of the current contents of our experience, even over tens of seconds or minutes, is presumably achieved by regions outside of the hippocampus.

There is now considerable evidence that a network of cortical regions supports the online representation of an ongoing event over these timescales (e.g. Baldassano et al., 2017; Hasson, Chen, & Honey, 2015). These long-timescale regions include the angular gyrus and posterior midline cortex (PMC) and they overlap extensively with the brain's so-called default mode network (DMN), a group of regions that are active during rest (Buckner, Andrews-Hanna, & Schacter, 2008; Raichle et al., 2001). The DMN is thought to underpin internally directed cognitive processes such as episodic memory, mind wandering and prospective thought (Andrews-Hanna, 2012; Spreng & Grady, 2010).

Within these regions, the PMC is consistently implicated in playing a central role in the online representation of lifelike events, both during perception and when retrieving the event in detail (Bird, Keidel, Ing, Horner, & Burgess, 2015; Chen et al., 2017; Oedekoven, Keidel, Berens, & Bird, 2017). Furthermore, the PMC appears to reside at the top of a hierarchy of brain regions that process events as they unfold. For example, Baldassano and colleagues (2017) showed that changes in patterns of brain activity within the PMC while participants watch an ongoing movie match closely with perceived scene changes.

However, the processes supported by the PMC and other cortical hubs of the DMN do not on their own lead to the establishment of durable memories. Instead, encoding of events into long-term memory requires intact hippocampal processing. Evidence for this comes from studies that have linked hippocampal activity with activity in regions of the PM network during successful memory encoding and retrieval (Ben-Yakov, Eshel, & Dudai, 2013; Ben-Yakov & Henson, 2018; Gordon, Rissman, Kiani, & Wagner, 2014; Leiker & Johnson, 2015; Ritchey, Wing, LaBar, & Cabeza, 2013; Staresina, Henson, Kriegeskorte, & Alink, 2012; Tompary, Duncan, & Davachi, 2016). Furthermore, two fMRI resting state studies of patients with amnesia, documented decreased connectivity between the hippocampus and a specific region within the PMC, the posterior cingulate cortex, in the patients compared to healthy controls (Hayes, Salat, & Verfaellie, 2012; Henson et al., 2016).

Taken together, it is known that hippocampal damage can impair memory for events, while real-time representations of events themselves appear to be supported by the PMC, as well as other regions of the DMN and sensory cortices. Functional interactions between the hippocampus and these same regions are related to memory performance in healthy adults, and decreased functional connectivity between the medial temporal lobe and PMC has been reported in patients with amnesia. In the present study, we investigate the brain regions supporting naturalistic event memory in a patient who suffered acute onset of a very severe episodic memory impairment. Assessment of his clinical brain scans revealed right-sided and possible milder left-sided thalamic

damage and a markedly small left hippocampus. We investigated whether functional changes could be detected within these areas of abnormality, whether there were functional changes in other regions involved in event processing, and whether there were changes in functional connectivity between the PMC and the rest of the brain when watching and retrieving lifelike events.

2. Case report

TF is a 75-year-old, right-handed retired household appliance engineer and model railway enthusiast, who presented to the Neurology Clinic with sudden and severely disabling global amnestic syndrome. Prior to this, he may have had a very slight decline in his memory, but not sufficient to interfere with his life in any way. There were no accompanying physical, neurological or visual symptoms and there was no antecedent illnesses or injury. His wife reported that evening before her birthday, he suddenly started repeatedly checking that the door was locked. The following morning, he could not remember where he had put his wife's birthday present and he asked her what date it was 3 times and couldn't remember he had even asked her each time.

It became clear that he was forgetting all new verbal information as well as most new events that he experienced. Two years after the onset of amnesia, he still often asks repeatedly whether they have had a particular meal in the day. He needs to be repeatedly reminded of activities planned for the day, but is able to maintain awareness of a task in which he is in the midst of participating, unless distracted part way through. In general conversation, his judgment does not seem impaired and he has a good road-crossing sense and he still criticizes other vehicle drivers. He is unable to plan a complex task and his wife has to get his clothes out for him, but he is then able to dress and wash without supervision. When walking in town, if distracted, he forgets where they have decided to go. He is able to understand quite complex paperwork and he makes appropriate comments, but as soon as it goes out of sight, he cannot recall any details and hence has ceased from doing any paperwork anymore. Apart from some very minor agitation initially, he has remained very placid about his predicament. There has been no confabulation, except possibly in estimating time

intervals, so for example when asked ‘when did you last drive?’, he often replies ‘last week’, even though he has not driven now for 2 years.

There is also some degree of retrograde amnesia, including the following: Immediately after the onset of amnesia, it had become apparent that he had forgotten all his computer passwords. He was unable to recall a local air crash 5 months prior to amnesia onset, despite this being a prominent news story. He didn’t recall that he and his wife had sold their greyhound dogs 2 years prior; he had completely forgotten a holiday 3 years prior; he kept forgetting that his wife’s parents had died 6 years prior; he forgot that his parents-in-law were in a home 9 years prior; he was unable to recall a cruise 13 years prior and he only very vague and partial recall of his 60th birthday fancy dress party 14 years prior to the onset of amnesia. The retrograde amnesia is however patchy and for example, from the onset, he was able to remember his grandchildren’s names who were born 5 and 7 years prior to the onset of amnesia. Despite the temporal disorientation, he knows where he is geographically. At 2 years after the onset of amnesia, he has lost his motivation and now sits a lot. Having been the main decision-maker in the household, he has withdrawn from decision-making and lost his previously characteristic critical mindset and now just accepts what his wife says.

He is an ex-smoker, but has no other vascular risk factors apart from his age.

Physical neurological examination was completely normal, in particular, his eye movements were normal and visual fields were normal.

On an Addenbrooke’s Cognitive Function (Version III) examination, he scored 76 out of 100. The most marked problem was with memory registration, after 5-minutes, being unable to recall any of 3 objects which he had repeated easily on immediate recall. He was unable to recall the date or the year, but he was able to name the hospital and floor and geographical location he was in. None of the elements of the 4-line name and address could be recalled at 5 minutes. Verbal fluency slightly reduced. He repeated ‘giraffe’ multiple times during the production of animal names verbal fluency test. He had no problem with naming or language or visuospatial abilities.

MRI brain scans showed a high T2 & FLAIR signal lesion in in the right medial thalamus which may extend to the mammillary body. There was possibly an additional smaller similar lesion in the left thalamus in an almost identical location (Figure 1). The scans also revealed the left hippocampus to be shrunken; with an overall medial temporal lobe atrophy scale of 3 on the Scheltens scale (range 0-4, with increasing score indicating greater atrophy; Scheltens et al., 1992). An intracranial CT Angiogram was normal and was not considered of sufficient resolution to be able to identify or exclude an artery of Percheron. Routine blood tests were normal except a moderately elevated total cholesterol of 5.9 and a moderately elevated ratio of 5.4 of total cholesterol to HDL cholesterol. A 7-day ECG monitor was normal. An echocardiogram was normal. A carotid & vertebral artery doppler ultrasound scan was normal.

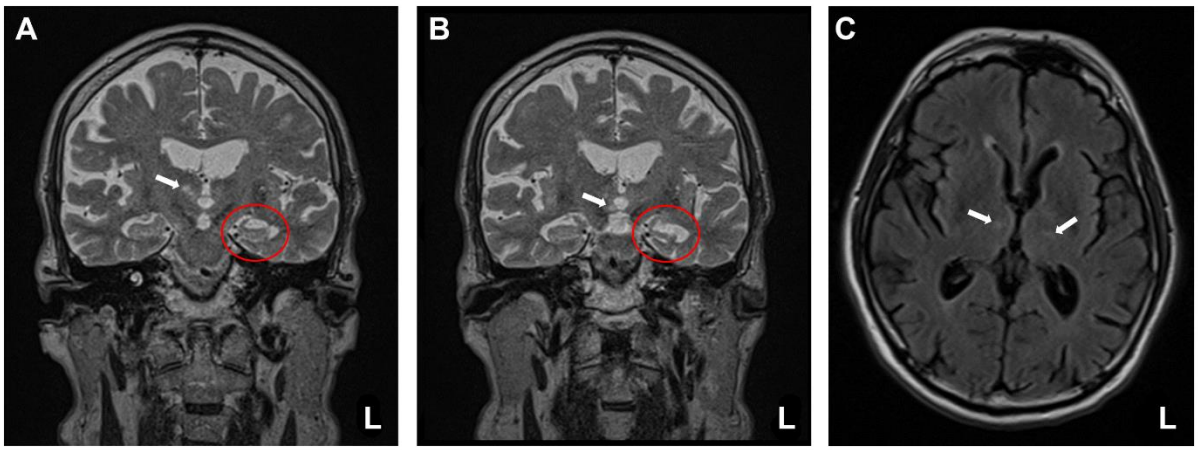

Figure 1: Panels A and B are T2-weighted coronal scans showing the shrunken hippocampus in the left hemisphere (highlighted by the red circle). Panel A additionally shows a subacute thalamic infarct in the right hemisphere and Panel B shows a right-hemisphere infarct at the level of the mammillary body (indicated by the white arrows). Panel C is a FLAIR scan showing the right-sided thalamic infarct and possibly a second infarct in a near-identical position in the left hemisphere (indicated by the white arrows). In all images the left hemisphere is shown on the right.

TF was started on clopidogrel. Two years after the event there has been no improvement.

2.1 Lesion analysis

We used Voxel Based Morphometry (VBM), a whole brain technique for characterizing regional volume and tissue concentration differences in structural MRI (Ashburner and Friston, 2000,

2001; Good et al., 2001; Mechelli, 2005). TF and 20 healthy controls (for demographic information, see section 3.1.1 below) underwent the acquisition of high-resolution T1-weighted structural images on a 1.5 T Siemens Avanto MRI scanner (FOV = 256 mm x 256 mm, 1 mm isotropic voxels, TR = 2.73s, TE = 3.57ms). A VBM analysis was conducted using the Computational Anatomy Toolbox (CAT12) in SPM12. During preprocessing, data were normalized to the T1 template, segmented into grey matter (GM), white matter (WM) and CSF and afterwards smoothed with an 8 mm FWHM Gaussian kernel. To compare TF's data to the controls, we used a two sample t-test. This treats the individual patient as a sample and is equivalent to a modified t-test, proposed by Crawford and Howell to compare a single case with a modestly sized control group (Crawford & Howell, 1998; see http://www.mrc-cbu.cam.ac.uk/people/rik.henson/personal/Henson_Singlecase_06.pdf for a discussion of this approach).

The VBM analysis identified TF had significantly grey matter reductions in the head and body of the left hippocampus and a superior region of the left thalamus (see Figure 2). This region of the thalamus is most strongly connected to the temporal lobes in healthy adults (Behrens et al., 2003; Fan et al., 2016)

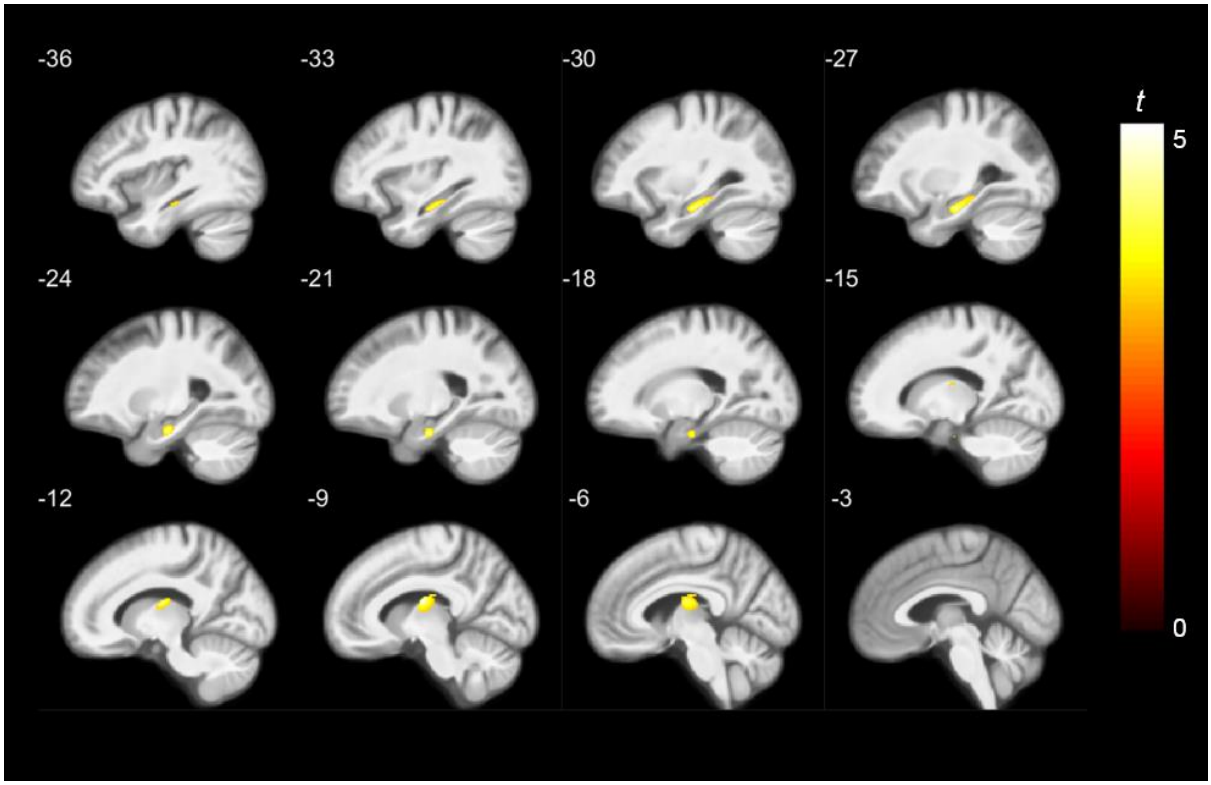

Figure 2: Structural VBM analysis showed decreased grey matter in TF in comparison to controls in left hippocampus and left thalamus (p<0.001, FWE-corrected for cluster size). Clusters are shown on the averaged normalised structural scans from the control group.

In addition, grey matter volume estimates were carried out for 130 separate brain regions using the Neuromophometrics atlas in CAT12. TF's left hippocampus was significantly smaller than the controls (hippocampal volume in TF relative to hippocampal volumes in the controls = 64%; z = -4.22, p < 0.0016 Bonferroni corrected). No other comparisons were close to significant after correcting for multiple comparisons. However, given that the clinical MRI scans detected abnormalities in the thalamus, we report the uncorrected values from this region. On the left, TF's thalamus was 39.3% smaller than the controls (z=-2.83, p=0.002 uncorrected for multiple comparisons), while TF's right thalamus was 11.1% smaller than the controls (z=-0.71, p=0.24).

2.2 Neuropsychological assessment

A first neuropsychological assessment, conducted by the author SA, took place at the Department of Neuropsychology at the Princess Royal Hospital, Haywards Heath, in November 2016 as part of TF's routine clinical care. This assessment consisted primarily of the Neuropsychological Assessment Battery (NAB, (Stern & White, 2003)). A second neuropsychological assessment, conducted by the author CO, took place at the University of Sussex in March 2017, using the Doors and People (Baddeley, Emslie, & Nimmo-Smith, 1994), the TOPF (Wechsler, 2009), Trail Making Tests A and B and a subtest of the VOSP (Warrington & James, 1991).

The results of the two neuropsychological assessments are reported in Table 1 and are summarized below.

Excluding memory, TF showed a normal performance regarding his general cognitive ability. Intellectual screening suggested average range ability consistent with prediction based on demographics and word knowledge (TOPF). Attention was within normal limits (NAB Digits, NAB Dots) and processing speed was average to above average (Trail Making Test A, NAB Letters &

Numbers). His perceptual processing skills were well within normal limits tested with a subtest of the VOSP for object perception (Object Decision) and the NAB Figure Copy test. An assessment of executive skills revealed normal performance on measures of planning (NAB Mazes) and divided attention/cognitive flexibility (Trail Making Test B).

TF's memory functions were severely impaired. Across subtests of the NAB memory module and the Doors and People, only visual recognition was within normal limits, while verbal recall, verbal recognition and visual recall were all severely impaired. The absence of meaningful learning curves on the repeated trials learning tasks (verbal and visual) suggested that repetition was of little benefit to the learning process.

Table 1: Neuropsychological test scores for TF

	Score	Percentile score
General cognitive ability		
TOPF IQ	36	95 (estimated FSIQ)
NAB Digits Forwards	36 (T)	8
NAB Digits Backwards	56 (T)	73
NAB Dots	50 (T)	50
NAB Numbers & Letters A Speed	66 (T)	95
NAB Numbers & Letters A Errors	39 (T)	14
NAB Numbers & Letters A Efficiency	63 (T)	90
NAB Figure Copy	55 (T)	69
NAB Mazes	70 (T)	98
Trail Making Test A	57 (T)	76
Trail Making Test B	44 (T)	27
Object Decision (VOSP)	20/20	
Memory		
D&P Total Age Related Score	20	<1
D&P Immediate Verbal Recall (People)	0	<1
D&P Delayed Verbal Recall (People)	0	
D&P Immediate Visual Recall (Shapes)	6	<1
D&P Delayed Visual Recall (Shapes)	2	
D&P Verbal Recognition (Names, Test A)	6	1
D&P Visual Recognition (Doors, Test A and B)	19	75
NAB Figure Recall	23 (T)	<1
NAB Figure % Retention	11 (T)	<1
NAB Total Immediate (List learning A)	38 (T)	12
NAB Short Delayed Recall (List learning A)	27 (T)	1
NAB Long Delay Recall (List learning A)	33 (T)	4
NAB Immediate Recognition (Shape Learning)	38 (T)	12
NAB Delayed Recognition (Shape Learning)	53 (T)	62
NAB Immediate Recall (Story Learning)	26 (T)	1
NAB Delayed Recall (Story Learning)	35 (T)	7
NAB Immediate Recall (Daily Living Memory)	35 (T)	7
NAB Delayed Recall (Daily Living Memory)	21 (T)	<1
NAB Memory Module Total	29 (T)	2

Legend: D&P: Doors & People Test, NAB: Neuropsychological Assessment Battery, TOPF: Test of Premorbid Functioning, VOSP: Visual Object and Space Perception Battery, FSIQ: Full scale IQ, T: *t*-scaled score

3. Experimental investigation

3.1 Methods

3.1.1 Participants:

Twenty healthy volunteers served as controls (age: mean = 73.55, SD = 7.56 sex: 11 female). They had on average 14.3 years of education (SD = 2.81) and an MMSE score of 29.2 (SD = 1.1). All had normal or corrected-to-normal vision. All participants gave written informed consent. The study was approved by the Brighton and Sussex Medical School's Research and Governance Ethics Committee and by the NRES Committee London - Queen Square and was conducted in accordance with relevant guidelines and regulations.

3.1.2 Stimuli

The stimuli consisted of 8 short videos lasting 43s on average (range 40 –46s). All videos were taken from www.YouTube.com and www.nsi-canada.ca/film-festival/. Each video described a short narrative and was presented without sound. The narratives centred around two main characters (7 videos) or an interaction of multiple characters (one video). Four videos took place inside of a building, two videos took place outside and two videos involved a change of location. The task was programmed in the Cogent 2000 toolbox (www.vislab.ucl.ac.uk/cogent_2000) using Matlab (Version 2013b, The Mathworks, Inc., Natick, MA, USA).

3.1.3 Experimental design

Participants took approximately 2 ½ hours to complete the study protocol. Before scanning, each participant completed a practice trial demonstrating the task as it would be shown in the MRI scanner, in which they were asked to watch an example video and describe it in as much detail as possible. They were then instructed to retrieve the videos silently once in the MRI scanner. They were also informed that they would be asked to describe each video after the MRI scan had finished.

During scanning, each video was presented in the middle of a black screen with a distinct title displayed above it (henceforth referred to as the "watching" phase). After a 12s ITI with a countdown of grey numbers, the retrieval phase for the preceding video began. The retrieval phase started with a 2s screenshot cue of the initial scene of the video. This was accompanied by the instructions "Please remember [Title of video]" presented in white text (to contrast with the black background). After the cue, the instructions faded to grey for the rest of the retrieval phase. The retrieval phase was partially self-paced: after 20s participants could end the retrieval phase with a button push using their right index finger—otherwise it ended automatically after 55s. Each retrieval phase was followed by a white fixation cross on a black background for 12s. Throughout the experiment, participants watched and then silently retrieved each video before having to remember the next video. For an illustration of the study design, see Figure 3.

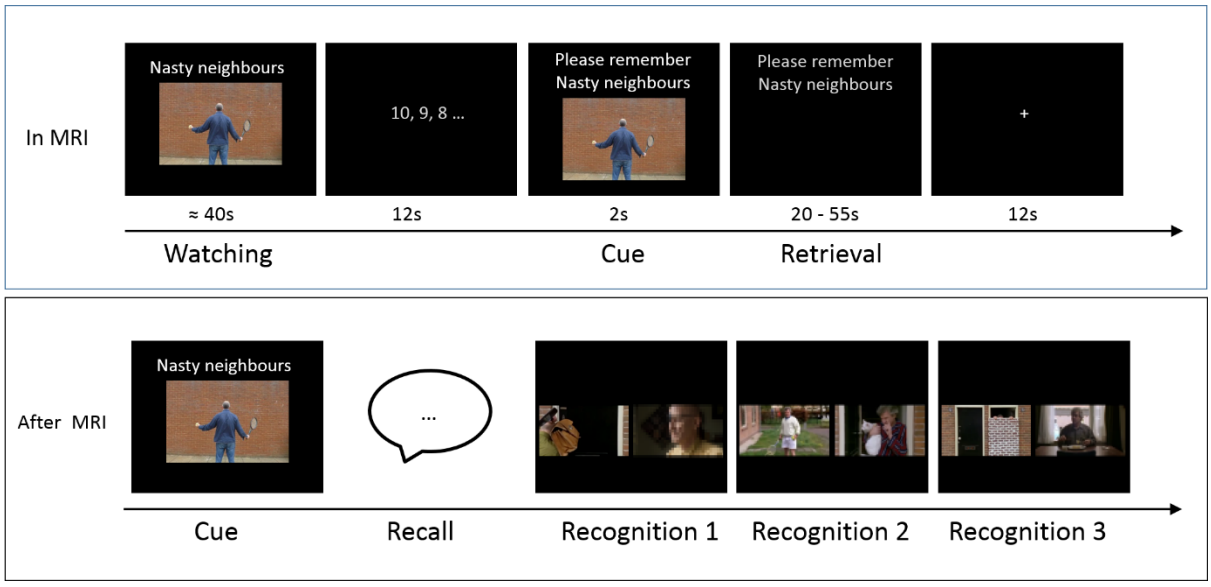

Figure 3: Study design. Participants watched a video and after a brief ISI were then cued to silently retrieve the video. Cues were the titles of the video and a screenshot showing the first frame. There were 8 videos in total. After scanning, they were asked to describe all 8 videos to the experimenter and answer a forced choice recognition test. (Images are pixelated for copyright reasons, participants looked at normal images in the recognition test).

After scanning, participants sat in a quiet room and were asked to freely recall each of the 8 videos in the same order as they had seen them in the MRI. Each video was cued with the title of the video and a screenshot of the first scene. Participants were asked to describe what happened in the video. If the description lacked detail, participants were encouraged to report more details. All descriptions were audiotaped. The free recall phase was followed by a forced choice recognition test, in which the participant was asked to choose which of two scenes had been part of the video watched in the scanner. The distractor items were chosen from parts of the same film that were not shown in the scanner. There were three trials for each video, thus the maximum score for the forced choice recognition task was 24.

3.1.4 Memory performance

Descriptions were later transcribed verbatim and each video's description was scored for the amount of independent details they contained. This provided a single score for memory performance and is an objective performance measure that can be used in parametric analyses of the imaging data. For each detail recalled, participants were given a score of 0, 0.5 or 1. The score was 0 if a detail was not mentioned at all, 0.5 if a detail was partially correct (e.g. "someone", "picks up something") and 1 if the detail was fully correct (e.g. "a man", "picks up bricks"). No points were awarded for details visible in the screenshot cue. There was no maximum amount of details to be recalled per video. This procedure is based on the scoring of widely used prose recall tests (e.g. Rivermead Behavioural Memory Test (Wilson, Cockburn, & Baddeley, 1991)). To ensure consistency across participants, all video descriptions were rated by one of the authors (C.O.).

3.1.5 Scanning protocol:

BOLD-sensitive T2*-weighted images were acquired during the functional run on a 1.5 T Siemens Avanto MRI scanner using gradient-echo EPI (voxel size = 3 x 3 x 3.6mm, FOV = 192mm x

192 mm, TR = 2.62s, echo time = 42ms, flip angle = 90 degrees, 35 ascending 3mm slices with a 0.6 mm gap).

3.1.6 Image preprocessing:

All analyses were carried out in SPM12 unless otherwise specified. DICOM files were first converted to NIFTI format. The structural image was coregistered to the first volume of the functional run and warped to the MNI template brain. Functional data were motion-corrected, slice-time corrected, normalized to the MNI template using the warp calculated for the structural image, and smoothed with an 8 mm FWHM Gaussian kernel.

3.1.7 FMRI analyses

We report a series of analyses where we first investigate the brain regions associated with watching and retrieving the videos in the healthy controls and then compare these to patient TF. Subject-specific parameter estimates relating to the conditions of interest were first calculated for each voxel. In the group analyses, these were then taken to the second-level and a random effects analysis was performed to identify consistent effects within the control group. To compare TF with the control group, we again performed 2-sample t-tests (see above). Since we are concerned with areas that are both recruited in the healthy brain as well as where responses are altered in TF, we restrict our comparisons to those regions were we find significant effects in the healthy participants. Analyses focus on overall levels of activity during watching and retrieval as well as functional connectivity analyses. For the latter analyses we use a PMC region as a seed for the following reasons: (1) it is the core hub of the DMN, (2) it is functionally connected with the hippocampus, which is abnormal in TF, (3) it has been associated with abnormal connectivity with the hippocampus following hippocampal damage, (4) it often exhibits hypometabolism in individuals with memory problems.

All analyses are cluster corrected for FWE at $p < 0.05$, using a height-defining threshold of $p < 0.001$. We additionally included two *a priori* regions of interest. In both the thalamus and hippocampus bilaterally (defined using the Automated Anatomical Labelling atlas; Tzourio-Mazoyer et al., 2002), we report clusters with a minimum of 5 voxels at a height-defining threshold of $p < 0.001$. The rationale for lowering the statistical threshold within these regions is that focal structural abnormalities were detected in TF for both the hippocampus and thalamus. Because the abnormalities were small, and that these are both heterogeneous structures, we carry out voxel-wise analyses rather than averaging the effects across the regions, since this capitalises on the relatively high spatial resolution of fMRI to detect functional changes.

3.1.8 Activation during watching and retrieval

At the first level, the preprocessed functional data were entered into a general linear model with two task regressors (watching and retrieval periods) as well as the six motion parameters calculated during realignment. In addition, data were high-pass filtered with a cut-off period of 128s. Parameter estimates for each condition and contrast were analysed at the second level with a one-sample t-test against a null hypothesis of 0 (watching > rest, retrieval > rest).

3.1.9 Functional connectivity during watching and retrieval

Connectivity estimates were obtained using the generalized PPI toolbox for SPM (McLaren, Ries, Xu, & Johnson, 2012). In particular, we were interested in the connectivity of the PMC with regions of the MTL during both watching and retrieval conditions separately. Our PMC seed was taken from the work of Allen and colleagues, who have made their resting-state maps available at: mialab.mrn.org/data/RSN_HC _unthresholded_tmaps.nii (Allen et al., 2011). The GLM for this analysis consisted of all the regressors described above in the section on GLM analysis, as well as the first eigenvariate of the time series within the PMC seed and the interactions of this seed with the

watching and retrieval regressors (see McLaren et al., 2012, for the details of how these regressors are computed).

3.2 Results:

3.2.1 Behavioural results

During scanning, TF did not press the button to indicate he had finished recalling the video on any of the trials (4/20 controls also did this). Regarding memory performance, TF was unable to recall any of the videos outside of the scanner whereas controls recalled on average 14.11 (SD± 2.73) details per video. On the 24-item screenshot recognition test, TF scored 14 out of 24, which is not significantly greater than chance performance (binominal test, p=0.27) and significantly below the performance of controls 23.85 (SD = 0.36) (t_{19} = 63.53, p < 0.001). In sum, TF demonstrated no retention of the videos he had watched in the scanner, his recall memory for the videos was completely at floor and his recognition was far below the level of the controls.

3.2.2 FMRI activation during watching and retrieval in the controls

In the controls, watching videos elicited a characteristic response pattern including extensive activation in the bilateral occipital and ventral temporal lobes, posterior parietal lobes and thalamus (Figure 4 and Supplementary Table 1). Deactivations were observed in middle and anterior cingulate, precuneus and bilateral middle frontal gyrus, which are part of the DMN. Retrieval of videos resulted in much more restricted bilateral medial occipital activations (Supplementary Figure 1 and Supplementary Table 2).

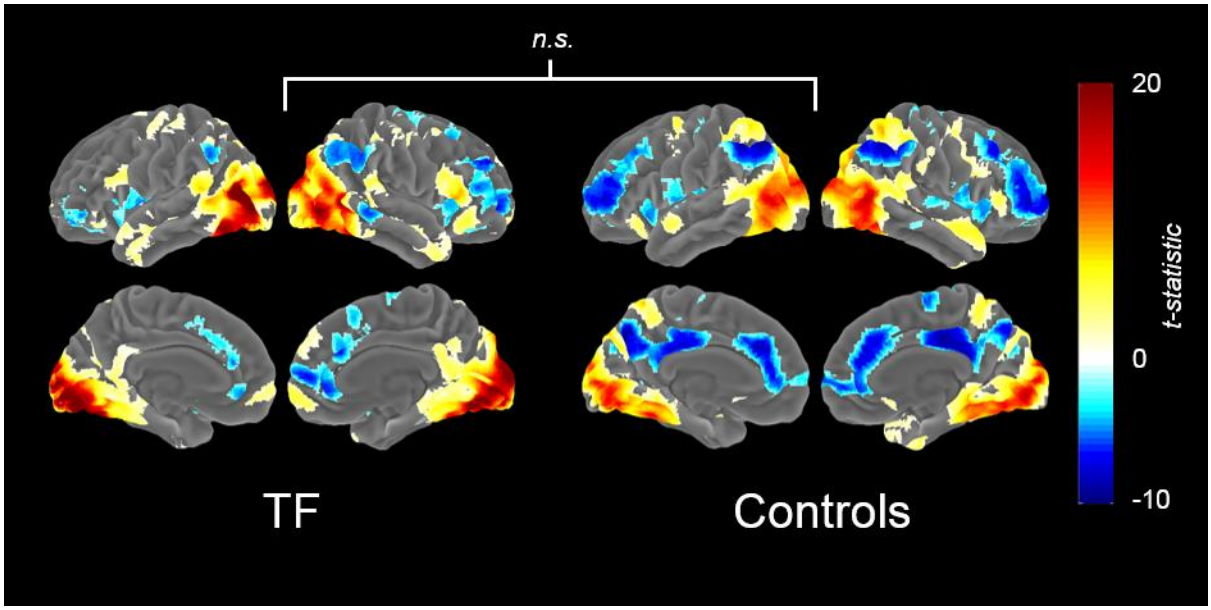

Figure 4: Regions activated during the watching phase compared with rest in the controls and TF. For controls, the effects illustrated are significant at $p < 0.05$ at the group level (FWE cluster corrected across the whole brain at a cluster-defining threshold of $p < 0.001$). For TF the within-subject effect are significant at a height threshold of $p<0.001$, but this is a fixed-effects analysis and is shown for illustrative purposes only. Formal comparison of TF and the control group using a procedure equivalent to a modified t-test revealed no significant differences. See text for details.

3.2.3 FMRI differences in activation during watching and retrieval: differences between TF and the controls

TF showed a qualitatively similar pattern of brain activity when watching the videos to the controls (Figure 4), suggesting that he attended to the videos while in the scanner. Within the areas activated in controls during the watching of videos, no significant differences were observed between TF and the controls. The comparison between TF and the controls during retrieval is limited by the fact that retrieval effects in the controls were restricted to midline occipital regions. No differences were seen in these regions between TF and the controls.

3.2.4 FMRI functional connectivity with the PMC in the controls

The PMC seed region was functionally connected with numerous brain regions during both watching and retrieval phases in the controls (Figure 5A). These included the medial frontal lobe,

precuneus, middle temporal gyrus, fusiform gyrus and the hippocampus. These areas are mostly associated with the DMN and also include ventral visual stream.

3.2.5 FMRI functional connectivity with the PMC: differences between TF and the controls

There was significantly less functional connectivity between the PMC and a region of the left hippocampus in TF compared to the controls during both the watching and retrieval phases (Figure 5B. Watch: $t_{peak}(19) = 4.2$, k=7 voxels, MNI coordinates: x = -27, y = -21, z = -21; Retrieval: $t_{peak}(19) = 7.1$, k=15 voxels, MNI coordinates: x = -27, y = -21, z = -21). This hippocampal region overlaps with the location identified as having significantly less grey matter volume in the VBM analysis (See Figure 2 above). No other significant differences were found between TF and the controls, despite the extensive functional connectivity between the PMC and other brain regions in the controls.

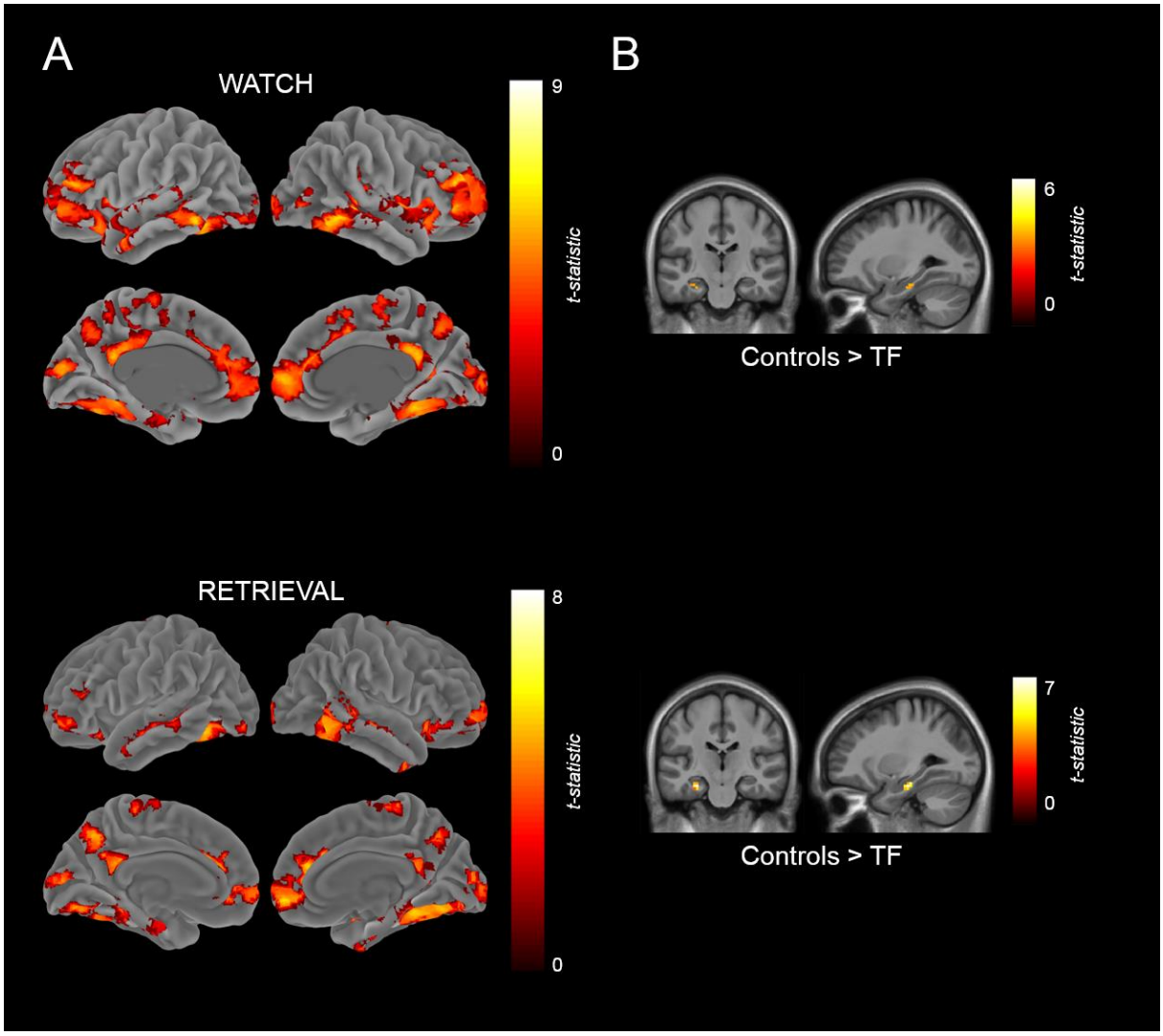

Figure 5: Functional connectivity with the PMC in the controls and the difference to TF in the hippocampal ROI during watching and retrieval phases.

3.2.6. Follow-up analysis 1: Hippocampal connectivity with other regions of the default mode network is not abnormal in TF

It is possible that abnormal connectivity between the PMC and the left hippocampal region in TF is due to the loss of grey matter in this region. Consequently, it could be that TF's functional connectivity with the left hippocampus and other nodes of the DMN is also reduced. To test this, we identified 3 more DMN regions from the same Allen et al., (2011) resting state analysis that the PMC seed region came from. These were the medial prefrontal cortex, the precuneus and a left angular gyrus. In the controls, there was significant functional connectivity between the left hippocampal

region and all of the DMN seed regions during both watching and retrieval phases (t-statistic 2.2-3.7, p-values 0.04-0.001). Critically however, there were no differences in functional connectivity between TF and the controls (lowest t-statistic for a difference = -1.69, p=0.11). Thus, despite all of the these DMN regions being functionally connected with the left hippocampal region in the controls, there was no significant difference in connectivity strength between TF and the controls, either when watching or retrieving the videos.

3.2.6. Follow-up analysis 2: Association between PMC and hippocampal connectivity and memory performance in the controls

Since TF, whose memory performance was at floor, showed a significant decrease in functional connectivity between a region of left hippocampus and the PMC, we hypothesised that the strength of functional connectivity between these regions in the controls might be related to memory performance. This was investigated in a follow-up analysis investigating the functional connectivity between the PMC region of interest and the left hippocampal cluster identified by the comparison between TF and controls reported above (specifically the cluster identified in the comparison TF < controls during retrieval, which overlaps but is slightly larger than the cluster identified during watching). The analysis did indeed identify a positive correlation between memory performance and the magnitude of functional connectivity between PMC and left hippocampus during the watching phase of the videos ($r = .483$, $p < 0.05$; see Figure 6). No such correlation was observed during the retrieval phase.

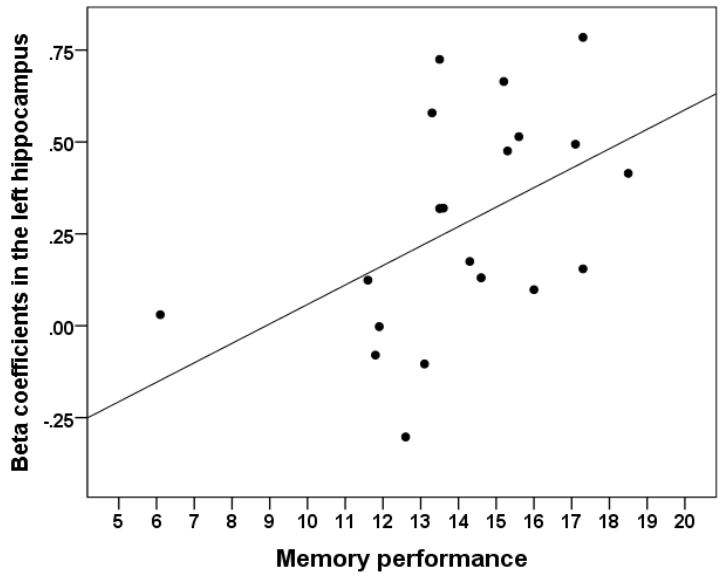

Figure. 6: Functional connectivity between PMC and a region of the left hippocampus while watching the videos correlates with memory performance in the controls. The left hippocampal region is the same area that shows abnormal functional connectivity in TF.

4. Discussion

In healthy adults, processing naturalistic events is associated with brain activity in a widespread network of regions, particularly those associated with the DMN. Successful encoding of these events into long-term memory and their subsequent retrieval is thought to depend on interactions between the hippocampus and several of these neocortical regions. To investigate these interactions, we scanned TF, an individual with a severe episodic memory impairment, while he watched and attempted to retrieve a series of short videos. His data were compared to a group of healthy older adults performing the same task. In line with his neuropsychological results, TF was unable to recall or recognise any of the videos outside of the scanner. To investigate the mechanism for this very poor level of performance, we first identified the brain regions that were engaged while healthy controls performed the task to then establish whether any of these regions were significantly under-activated in TF. The main finding was that in the controls, the PMC was functionally connected with the left hippocampus both when watching and retrieving the videos, whereas this connectivity was significantly reduced in TF. Furthermore, in the controls, the strength of functional connectivity between these two regions when the videos were being watched correlated with subsequent ability to remember the videos.

Outside of the laboratory and clinic, TF retained the ability to understand quite complex paperwork as well as everyday situations, which is consistent with his well-preserved working memory and cognitive function in other domains. Such a sharp discrepancy between immediate memory for even complex information and delayed retention of the same material has been previously noted in patients with acute amnestic syndromes and stands in contrast to patients with Alzheimer's disease (Baddeley & Wilson, 2002).

Comprehending a video is likely to engage the same processes as real-world interactions. Incoming sensory information has to be perceived and linked to prior knowledge to set up an "event model" (Zacks, Speer, Swallow, Braver, & Reynolds, 2007). Accordingly, it is perhaps unsurprising that the network of brain regions showing both activation and deactivation effects while watching

the videos did not differ between TF and the age-matched controls. Surprisingly, there were also no significant activation differences between TF and the controls during the retrieval periods. However, even in the controls, there was only a small posterior midline region in the occipital lobe that showed a significant effect during retrieval. This contrasts with our previous findings using a similar task in young adults (Bird et al., 2015; Oedekoven et al., 2018) and suggests that older adults recruit a less consistent network of brain regions during retrieval, resulting in more variability across the group.

Next, we investigated functional connectivity between a bilateral region of PMC and the rest of the brain when watching and retrieving the videos. We chose this region as it is a core component of the DMN (Greicius, Srivastava, Reiss, & Menon, 2004), it is closely functionally connected with the hippocampus (Maguire, Mummery, & Buchel, 2000), it is associated with abnormal connectivity with the hippocampus following hippocampal damage (Henson et al., 2016) and it often exhibits hypometabolism in patients with memory problems (Aupee et al., 2001). Furthermore, the region is consistently implicated in representing the content of video clips during memory encoding and retrieval (e.g. Bird et al., 2015; Chen et al., 2017). In line with these previous studies, the regions functionally connected to the PMC in our task overlap substantially with the DMN and additionally include ventral visual stream. Strikingly, when comparing TF with the controls, the only consistent effect was a reduction in functional connectivity between a region in the left hippocampus and the PMC (Figure 4B). Follow up analyses demonstrated that the same region of the hippocampus did not show abnormal functional connectivity with other regions associated with the DMN (medial prefrontal cortex, precuneus and angular gyrus).

Given the known importance of the medial temporal lobes in memory, and the fact that TF has significant grey matter volume loss in the left hippocampus, it is perhaps not surprising that effects should be found here. However, it might also be predicted that we would see more widespread effects. Diaschisis – where focal brain damage causes effects on anatomically connected regions of the brain – has been well-documented in humans and animal models (Carrera & Tononi,

2014). In rats it has been shown that hippocampal lesions cause cell loss in the retrosplenial cortex (Albasser, Poirier, Warburton, & Aggleton, 2007). Yet despite TF's very severe memory impairment, there were no consistent alterations in connectivity between the PMC seed region and elsewhere in the brain.

Our findings extend those of Henson et al., (2016) who investigated resting state functional connectivity differences in 6 patients with hippocampal damage compared with a group of healthy age-matched controls. The authors found that out of 8 regions associated with the DMN, only the connectivity between the hippocampus and PMC was significantly impaired. In our study, a reduction in connectivity is seen while the participants are engaged in a naturalistic episodic memory task.

Although our fMRI findings highlight the abnormal functional connectivity between the hippocampus and PMC, TF's memory impairments are highly likely to be precipitated by a stroke affecting the thalamus. The fact that this region was not identified in our analyses reveals both strengths and limitations of using functional MRI to identify the neuroanatomical substrates of cognitive processes. The standard cognitive neuropsychology approach would be to associate the observed cognitive impairment (in episodic memory) with the observed brain lesion (to thalamic regions on the left and right and to the left hippocampus where there was also volume loss). However, in the healthy participants, the thalamic regions damaged in TF were not correlated with periods of the task. So, while there is substantial evidence that the various nuclei of the thalamus and intrathalamic white matter tracts play necessary roles in episodic memory (Aggleton, Dumont, & Warburton, 2011; Carlesimo, Lombardi, & Caltagirone, 2011; Cipolotti et al., 2008; Danet et al., 2015) , the present study does not shed further light in these roles.

It would be unusual that stroke resulting in such small and subtle lesions within the thalamus would result in a very severe amnesic syndrome affecting both anterograde and retrograde memories and verbal and visual material. Although such lesions can affect verbal and/or visual material, the deficits are not usually very severe, and they do not normally result in retrograde

amnesia (Carlesimo et al., 2011; Danet et al., 2015; Van der Werf et al., 2003). We speculate that the volume loss in TF's left hippocampus, and possibly the region of the left thalamus, is long-standing in nature, perhaps due to a birth injury or sub-clinical Alzheimer's disease. As a result of this, TF may have compensated by relying for some time on right-hemisphere based memory circuits. Such functional reorganisation is seen in patients with longstanding unilateral hippocampal sclerosis due to epilepsy (Richardson, Strange, Duncan, & Dolan, 2003). TF's right-hemisphere infarct may therefore have effectively resulted in a bilateral disruption of memory circuits.

Our findings constrain the conclusions that can be reached from fMRI studies using videos as stimuli that have included young adults as participants (e.g. Bird et al., 2015; Chen et al., 2017; Oedekoven et al., 2017). In general, these studies have reported effects within the DMN. While these regions likely support the online representation of the contents of the video, they are not sufficient for the encoding or retrieval of memories – this requires interactions with the hippocampus (see also, Marr, 1971; McClelland et al., 1995; Schapiro et al., 2017; Teyler & DiScenna, 1986; Treves & Rolls, 1994). Further support for this view comes from recent studies showing that during free viewing of an extended video, at the end of event "segments", activity in the hippocampus showed a transitory increase in activity, argued to reflect the encoding of that particular event in to long-term memory (Baldassano et al., 2017; Ben-Yakov & Henson, 2018).

In summary; our results provide new evidence for the importance of interactions between the left hippocampus and the PMC when both watching and successfully retrieving extended naturalistic events. In a group of healthy older adults, the PMC was functionally connected to the hippocampus and other regions of the DMN and ventral visual stream while the participants watching and then retrieved extended video clips. In TF, an individual with dense amnesia and grey matter loss in the thalamus and left hippocampus, the functional connectivity between the PMC and hippocampus was significantly reduced. Furthermore, the functional connectivity between these two regions during encoding was modulated by memory strength in the healthy adults. The interactions between the two regions enable multimodal representations of the contents of an

event, supported by the PMC, to be encoded and retrieved from memory by dedicated processes supported by the hippocampus.

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